Claim 12, line 3, please change "a protein of" to - E2 -.

Claim 13, lines 3-4, please change "a protein of" to - E2 -.

Claim 14 (Twice Amended) A protein having a molecular weight of about 24 kd and capable of specifically binding to E2 of hepatitis C virus, for use as a pharmaceutical.

Claim 17, line 3, please change "a protein of" to - E2 -.

Remarks

Claims 2-4, 6-14, and 17 were pending. Claims 2-4, 6-14, and 17 were rejected in the Final Office Action. The Applicant respectfully requests that the Examiner reconsider and withdraw the rejections in view of the foregoing amendments and arguments that follow.

Preliminarily, Applicant notes with appreciation the withdrawal of several of the rejections from the previous Office Action. The Final Office Action, however, included a new ground of rejection of the claims. The new ground of rejection was not necessitated by any amendment to the claims made in the previous Response and Amendment, nor based upon information submitted in an Information Disclosure Statement. The finality of the present Office Action is, thus, premature. *See* MPEP § 706.07(a).

Specifically, the Examiner alleged that

> The claims have been amended to recite a process for the preparation of a protein "capable of specifically binding a protein of hepatitis C virus."

Claim 4, however, has always been directed to a process. Claims 4 and 13 were previously dependent upon claim 1. Claim 1, canceled in the response filed January 5, 2000, recited that the

can be found in the claims as originally filed and page 1, lines 4-5, of the application as originally filed.

Rejection under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1-15 and 17 under § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention was maintained for claims 2-4 and 6-10. According to the Examiner, the disclosure fails to teach the minimum length of the fragment that binds to HCV. The Examiner also maintains that the disclosure fails to teach or to provide guidance as to what substitutions, insertions or deletions would be expected to retain functional equivalency in the claimed variant. The Examiner asserts that a functional equivalent is defined in the specification as one which "at least binds to E2 protein of HCV." (See page 3 of the Final Office Action.) Moreover, according to the Examiner, the disclosure fails to teach what other HCV proteins the claimed protein or variant or fragment would be expected to bind to and, thus, the disclosure fails to teach the function of the protein or variant or fragment as claimed and the claims are indefinite. Applicant respectfully traverses this rejection.

Applicant respectfully submits that it is not necessary to teach the minimum length of the fragment, or to provide the substitutions, insertions, or deletions expected to comply with 35 U.S.C. § 112, second paragraph. All that is required is that the claims define the subject matter with a reasonable degree of particularity and precision. The Examiner should permit some latitude in that regard. MPEP 2173.02. Indeed, functional limitations do not, in themselves, render claims

improper. *In re Swinehart*, 169 USPQ 226 (CCPA 1971).

As observed by the Examiner, functional equivalent is defined as "at least binding to E2 protein of HCV" (see page 3 of the Final Office Action). The claims as amended recite that the protein, or functionally equivalent variant or fragment, binds E2. The specification sets forth ample guidance for assaying E2 binding. See, for example, page 20, line 23, through page 23, line 26, of the application as filed. The minimum length of the fragment binding E2 can be readily determined by one of ordinary skill in the art. Similarly, functionally equivalent variants can also be readily determined by one of ordinary skill in the art.

The Examiner next argued that it is unclear if the variant or fragment of claim 4 is to be subjected to the same steps as those of the protein, or if it is to be further prepared from the protein after it is prepared by the recited steps. The Examiner requested clarification. Applicant respectfully submits that both options are covered by claim 4. See, for example, page 4, lines 9-14 and page 5, lines 31-37, of the application as filed. Coverage of both options does not render the claim indefinite.

The rejection of the claims in view of the recitation "functionally unglycosylated" was also maintained. Applicant respectfully traverses the rejection based on this ground.

The language "functionally unglycosylated" is adequately described in the specification, and is otherwise know by those of ordinary skill in the art. For example, when describing the characteristics of the 24 kd protein, the Applicant set forth precisely how those of ordinary skill can determine whether the polypeptide of the invention is "functionally unglycosylated:"

> Our experiments have shown that the 24kd protein is functionally unglycosylated. Treatment with glycosidases does not affect the ability of the 24kd protein to bind to the E2 protein and does not appear significantly to reduce the molecular weight. We infer therefore that, if the protein is glycosylated at all, glycosylation must be restricted to a small number of sugar moieties and is not necessary for functional activity of the protein.

"Functionally unglycosylated", therefore, means that glycosylation of the protein is not required for function of the protein. Accordingly, the Applicant respectfully requests that the rejection based on this ground be withdrawn.

The Examiner next argued that claim 6 was not amended to delete "hyperexpression," and is therefore indefinite. Claim 6 has been amended accordingly. The Applicant respectfully requests that the rejection based on this ground be withdrawn.

With respect to claims 8 and 9, the rejection was maintained because it allegedly remains unclear whether the applicant intends that the claimed process incorporate part or all of the procedural **steps** that are taught in the specification. The claims, however, recite "procedure" rather than "step." Indeed, those of ordinary skill would consider that "at least one" refers to the number of procedures rather than the number of steps within the procedure.

Applicant respectfully requests that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejection under 35 U.S.C. § 112, First Paragraph

The rejection of claims 2-4, 6-10, 13 and 17 under § 112, first paragraph, was maintained for claims 2-4, 6-14, and 17. Specifically with respect to claims 2-4, 6-10, 13, and 17, the Examiner alleged that the Applicant failed to address the rejection of these claims in the previous

office action, and, thus, maintained the rejection for the reasons set forth therein. The Applicant respectfully disagrees, and requests that the rejection of these claims be withdrawn.

Applicant addressed the rejection of claims 2-4, 6-10, 13, and 17 in parity with the rejection in the previous office action. In asserting the rejection, the Examiner argued the following.

> As described *supra*, claims 1-4, 11-15, and 17 recite a protein capable of specifically binding a protein of hepatitis C virus (HCV) or a 'functionally equivalent variant or fragment thereof'. Because the metes and bounds of 'functionally equivalent' and 'fragment' are **unclear**, the skilled artisan would be unable to make the invention as claimed. Similarly, because the meaning of 'functionally unglycosylated' as it is applied to claim 2 is also **unclear**, the skilled artisan would be unable to make the invention as claimed.
>
> As described *supra*, the definition, order, and frequency of the steps of ammonium sulfate precipitation, hydrophobic interaction chromatography, and acetone precipitation recited in claims 7, 8, and 9 are **indefinite**; thus, the skilled artisan would be unable to practice the claimed process. Similarly, the skilled artisan would be unable to practice the process of claim 10 due to the **indefiniteness** of the recited steps.

(See pages 7-8 of the Office Action dated September 14, 1999. Bold emphasis supplied.) Clearly, the Examiner was basing the enablement rejection of these claims on their alleged indefiniteness.

Applicant responded as follows.

> The § 112, first paragraph, rejection is divided, essentially, into two parts. The first part is directed to claims 1-4, 11-15 and 17, and appears to be based solely on arguments made regarding the second paragraph rejections, *supra*. Indeed, the Examiner merely reiterates and/or refers to arguments made with regard to indefiniteness in maintaining this part of the enablement rejection. In view of the foregoing arguments and amendments, applicant respectfully submits that these rejections have been obviated and requests that they be withdrawn.

(See page 14 of the Response and Amendment filed January 5, 2000.) Thus, Applicant did address the Examiner's enablement rejection -- i.e., by responding to the indefiniteness rejections.

Applicant requests that the Examiner withdraw this rejection.

While admitting that the disclosure is enabled for *in vitro* applications, the Examiner maintained the rejection of claims 11 and 12 asserting that the disclosure is not enabling for *in vivo* application. The Examiner again relied upon Rice in support. According to the Examiner, Rice teaches that CD81 does not necessarily have any therapeutic application *in vivo*, and further teaches that any potential therapeutic application will depend on many unknowns. Applicant respectfully traverses this rejection

First, claim 12 is not directed to therapeutic compositions but, rather, to a "pharmaceutical composition." A pharmaceutical composition can also be used for *in vivo* diagnostics. Thus, Applicant requests that the rejection of claim 12 be withdrawn.

Regardless, therapeutic application *in vivo* is enabled. One of the "unknowns" Rice cites as of "paramount importance" is whether CD81 is critical for HCV infection. In the previous Response and Amendment, Applicant demonstrated that the protein of the invention is critical for HCV infection. For example, Applicant describes analyzing various cell types, from various species, using FACscan and Western blot for the presence of HCV receptor (page 23, line 28 - page 24, line 18, of the application as filed). The results of these studies demonstrate that the species distribution of the 24kd protein matches that of HCV infection susceptibility, *i.e.*, species resistant to infection do not have the 24 kd protein. Applicant also demonstrates that the 24kd protein is a transmembrane protein, suggesting that it is a cellular receptor (page 3, lines 21-23; page 23, line 28 - page 26, line 32, of the application as filed). These results support the conclusion reached by

the Applicant that the 24kd protein is critical to HCV infection (page 2, line 38 - page 3, line 2, of the application as filed). That the protein has therapeutic application is therefore without question.

The Examiner also maintained the rejection arguing that, while not encompassing monoclonal antibodies, Applicant's claimed protein would encompass fragments of monoclonal antibodies. As discussed below, discussion incorporated herein, Applicant must disagree with the Examiner's interpretation. Regardless, this would not render Applicant's claims non-enabled. The Examiner is basing non-enablement on her requirement that the antibodies neutralize HCV infectivity *in vivo*. Claim 11, however, recites that the "protein . . . or functionally equivalent variant or fragment thereof" be in an amount effective "to **reduce** infectivity of the virus." Applicant respectfully requests that this rejection be withdrawn. If it will advance prosecution, however, Applicant will consider canceling claim 11 to pursue in a continuation application.

New Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 2-10 and 13 were rejected under § 112, second paragraph, as allegedly being incomplete for omitting an essential step. The allegedly omitted step is the binding step. Applicant respectfully submits that this step was implicit in the claims. Nonetheless, to advance prosecution, claims 4 and 10 have been amended to recite the binding step. Applicant respectfully requests that the rejection be withdrawn.

Rejection of claims 1 and 17 under 35 U.S.C. § 102(b)/103

The rejection of claims 1 and 17 under § 102(b) as anticipated by or, in the alternative, under § 103 as obvious over, Mehta et al. was maintained for claim 17. According to the Examiner,

absent some evidence to the contrary, any fragment of a larger monoclonal antibody which is about 24 kD and which retains binding specificity to HCV would anticipate the claimed invention. Applicant respectfully traverses this rejection.

The claims are not directed to "24 kD fragments" but to fragments or variants of a 24 kD **protein**. Regardless, the Examiner has not established the existence of 24 kD fragments of antibodies, nor the motivation to prepare the same. The Examiner cannot simply argue that such fragments *could* be produced. Such an argument does not meet the standards for anticipation or obviousness. If the Examiner is relying upon personal knowledge, she is requested to submit an affidavit or other proof under 37 CFR § 1.104(d)(2), or withdraw this rejection.

CONCLUSION

For the foregoing reasons, Applicant requests that claims 2-4, 6-14, and 17 be allowed at this time. A notice of allowance is earnestly solicited. If the Examiner thinks a telephonic discussion would be helpful, she is asked to contact the undersigned at 215-564-8352.

Respectfully submitted,

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ABSTRACT

A 24kd protein capable of binding the E2 envelope protein of hepatitis C virus (HCV), and functionally equivalent variants or fragments of the 24kd protein, are disclosed. Processes for production and purification of the 24kd protein, and functionally equivalent variants or fragments thereof, are also disclosed.